

Evaluation of sulphasalazine in the treatment of spondyloarthropathies

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Abstract

Sulphasalazine has been shown to have an effect in patients with spondyloarthropathies, but the clinical indication for its use is controversial and its long term effect has not yet been evaluated. Treatment with sulphasalazine was analysed retrospectively in a group of 372 patients with a wide range of spondyloarthropathies to determine subsets of patients showing differential effects of the drug. One hundred and one patients received sulphasalazine at a mean daily dose of 2 g (ankylosing spondylitis, 54 patients; psoriatic arthritis, 21 patients; reactive arthritis, four patients; arthritis related to inflammatory bowel disease, six patients; undifferentiated spondyloarthropathy, 16 patients). A comparison between treated and untreated patients suggests that only patients with active and severe disease were treated whatever the precise diagnosis or the amount of axial disease in the spondyloarthropathy.

After six months of treatment improvement was noted in 59 patients unrelated to their subgroup or amount of axial disease. After a mean follow up of 20 months, 37 patients were still receiving treatment, 33 had discontinued the drug because of inefficacy, 14 because of side effects, six because of remission of the disease, and 11 for other reasons. Comparison between the beginning and end of treatment showed a statistically significant decrease in morning stiffness, erythrocyte sedimentation rate, and daily dose of non-steroidal anti-inflammatory drugs (NSAIDs).

It is concluded that: (a) a low percentage of patients with spondyloarthropathy have active disease requiring treatment with sulphasalazine despite the use of NSAIDs (27% in this study); (b) in this subgroup of patients sulphasalazine seems to be of clinically relevant benefit in 59%; and (c) this benefit does not seem to be correlated with either the precise diagnosis of spondyloarthropathy or the amount of axial disease.

(*Ann Rheum Dis* 1992; 51: 955-958)

The spondyloarthropathies consist of several diseases, including reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease, a subgroup of juvenile chronic arthritis, and ankylosing spondylitis, the latter being the prototype of this group of interrelated disorders.^{1,2} Classification criteria for the whole range of spondyloarthropathies have been proposed to encompass not only patients with these well defined diseases but also patients

with undifferentiated spondyloarthropathy.^{3,4} Within the group of spondyloarthropathies patient classification may be based on either the precise diagnosis—for example, ankylosing spondylitis, psoriatic arthritis—or the clinical presentation of the disease (axial disease, articular peripheral disease, enthesiopathic lesions, extra-articular symptoms). The monitoring and treatment of these diseases are related more to their clinical presentation than to their precise diagnosis.⁵

Sulphasalazine was developed and manufactured to cure rheumatoid arthritis by eliminating the putative cause, a group B streptococcal intestinal infection. After a temporary demise sulphasalazine gained a position as a second line disease modifying drug mainly through the work of McConkey *et al.*⁶ Sulphasalazine has been accepted as the drug of choice in the treatment of inflammatory bowel disease.⁷ Although the stimulus for using sulphasalazine in the treatment of spondyloarthropathy did not derive directly from its use in patients with rheumatoid arthritis, there are several arguments for considering it: (a) the common association between inflammatory bowel disease and spondyloarthropathy²; (b) the description of inflammatory lesions in the ileum of patients with spondyloarthropathy,^{8,9} and (c) the reported association between disturbances in bowel flora and ankylosing spondylitis.¹⁰ Much of the rationale postdated the early clinical studies.¹¹ Since 1984 a number of workers have shown that sulphasalazine may be effective in the treatment of spondyloarthropathies. Meta-analysis carried out on five randomised controlled trials¹²⁻¹⁶ suggests that sulphasalazine is a safe and effective drug in the short term (three to six months) treatment of ankylosing spondylitis.¹⁷ Other studies suggest that a beneficial effect of sulphasalazine might be observed not only in ankylosing spondylitis but also in the articular symptoms of reactive arthritis¹⁸ and psoriatic arthritis,^{19,20} and on the extra-articular symptoms of spondyloarthropathies such as psoriasis²¹ and uveitis.²²

All these clinical trials were short term (three to six months) and were conducted in selected patients. Therefore to identify a subgroup of patients with spondyloarthropathy who might preferentially respond to sulphasalazine we retrospectively analysed the patients monitored in our department by comparing those who did and did not receive sulphasalazine and those who did and did not respond to treatment. In the group of patients who received sulphasalazine the long term effect of the drug was evaluated by using life table analysis to calculate

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Accepted for publication
4 February 1992

the percentage of patients receiving treatment after some time.

Patients and methods

The files of all inpatients or outpatients consulting two of the authors (BA and MD) in the department of rheumatology of Cochin Hospital in the period 1982-91 with a diagnosis of spondyloarthropathy were examined. All the patients who met the criteria for spondyloarthropathy^{3 4} were selected for study.

The basic disease related information was derived from the inpatient and outpatient files and consisted of the following: age, sex, HLA-B27 positivity, subgroup of spondyloarthropathy (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease, undifferentiated spondyloarthropathy), the rheumatological manifestations of spondyloarthropathy (axial disease, peripheral disease, enthesiopathy), the extra-articular features (uveitis, psoriasis, inflammatory bowel disease), severity of the spondyloarthropathy (hip disease, erosive arthritis), and treatment given.

For the patients who had received sulphasalazine the following parameters were noted: time of start of treatment relative to the onset of disease, duration of treatment, efficacy variables at entry and at the last visit (including night wakings due to pain, presence of morning stiffness, erythrocyte sedimentation rate (mm

in first hour), platelet count, and the daily dose of non-steroidal anti-inflammatory drugs (NSAIDs) necessary for patient comfort according to a scoring reported previously.¹² a score of 10 is given to a daily intake of 100 mg indomethacin). A patient was considered as responding to treatment with sulphasalazine if after the first six months of treatment the decision to continue treatment for a longer period was taken. The reason for stopping treatment was noted as inefficacy, toxicity, remission of the disease, event unrelated to treatment or unknown reason.

Statistical analysis was carried out to compare the characteristics of the patients who did or did not receive sulphasalazine. In the group of patients who had received sulphasalazine changes in the efficacy variables during treatment were analysed using the χ^2 test for the qualitative variables and by the non-parametric Wilcoxon rank sum test for intragroup comparison of the quantitative variables. The threshold of significance adopted was 5% (two tailed). The treatment termination curves were evaluated by the Kaplan-Meier method.

Results

PATIENTS AND STUDY COURSE

Between June 1982 and May 1991 372 patients attending this department fulfilled the criteria for diagnosis of spondyloarthropathy. Sulphasalazine was given to 101 patients (27%) at a mean (SD) daily dose of 2.2 (0.6) g.

At the time of the study 37 patients were still receiving treatment; the other 64 patients had discontinued treatment with sulphasalazine for the following reasons: inefficacy, 33 patients; side effects, 14 patients; remission, six patients; other reasons, 11 patients.

CHARACTERISTIC OF SPONDYLOARTHROPATHY WITH RESPECT TO TREATMENT WITH SULPHASALAZINE

Table 1 summarises the main characteristics of the patients with respect to treatment with sulphasalazine. The patients who received sulphasalazine had more severe disease as hip disease and erosive arthritis were more commonly observed than in patients who did not receive sulphasalazine (16% v 7%, $p=0.01$ and 21% v 9%, $p<0.01$ respectively).

TREATMENT WITH SULPHASALAZINE

Table 2 summarises the changes in the efficacy variables between the start of treatment and the last visit while receiving treatment. Most of the patients had active disease when sulphasalazine treatment was initiated despite treatment with an optimum dose of NSAIDs. After treatment all these variables improved allowing a reduction in the daily intake of NSAIDs.

After the first six months of treatment, treatment was considered efficient in 59 of 101 patients. Table 3 summarises the characteristics of the patients who did and who did not respond to treatment. In these analyses a responder was defined as a patient who continued

Table 1 Characteristics of the 372 patients with spondyloarthropathies who did and did not receive sulphasalazine

Patient characteristics	Sulphasalazine treatment*		p Value†
	Yes (n=101)	No (n=271)	
Mean (SD) age (years)	35 (15)	36 (13)	NS
Sex (F/M)	35/66	91/180	NS
HLA-B27 positive/negative	69/28	160/66	NS
Subgroup of spondyloarthropathy			
Ankylosing spondylitis	54	155	
Psoriatic arthritis	21	62	
Reactive arthritis	4	16	NS
Inflammatory bowel disease related arthritis	6	7	
Undifferentiated spondyloarthropathy	16	31	
Rheumatological manifestations			
Axial disease (yes/no)	83/18	216/55	NS
Peripheral disease (yes/no)	78/23	160/111	NS
Enthesiopathy (yes/no)	75/26	158/113	<0.01
Severity of spondyloarthropathy			
Hip disease (yes/no)	16/84	20/249	0.01
Erosive arthritis (yes/no)	21/77	25/243	<0.01
Extra-articular features			
Uveitis (yes/no)	19/82	31/240	NS
Psoriasis (yes/no)	30/71	74/196	NS

*Values given are either the number of patients with the variable or the mean (SD).

†Statistical significance determined by the χ^2 test for the qualitative variables and the non-parametric Wilcoxon test for the continuous variables. NS=not significant.

Table 2 Efficacy variables in patients with spondyloarthropathy at the start of treatment with sulphasalazine and at the last visit while receiving treatment

Variables*	Start of treatment	Last visit while receiving treatment	p Value†
Nocturnal awakenings due to pain (n=53)	33	16	<0.01
Morning stiffness (n=52)	44	31	<0.01
Mean (SD) erythrocyte sedimentation rate (mm/first hour) (n=51)	39 (30)	28 (20)	<0.01
Mean (SD) NSAIDs (daily scoring) (n=74)‡	11 (7)	9 (8)	<0.01

*n=number of patients in whom the data on the parameter were available at the start of sulphasalazine treatment and at the last visit while receiving treatment.

†Statistical significance determined by the paired χ^2 test for the qualitative variables and by the non-parametric Wilcoxon test for the quantitative variables.

‡NSAIDs=non-steroidal anti-inflammatory drugs.

Table 3 Characteristics of the patients with spondyloarthropathy who did and did not respond to treatment with sulphasalazine

Variables	Responder to sulphasalazine*		p Value†
	Yes (n=59)	No (n=19)	
Age (years)	40 (13)	37 (13)	NS
Sex (M/F)	35/24	16/3	0.047
HLA-B27 positive/negative	39/17	13/6	NS
Subgroup of spondyloarthropathy			
Ankylosing spondylitis	33	11	
Psoriatic arthritis	12	3	
Reactive arthritis	12	1	NS
Inflammatory bowel disease related arthritis	5	0	
Undifferentiated spondyloarthropathy	8	4	
Rheumatological manifestations			
Axial disease	13	8	
Peripheral disease	10	2	NS
Enthesiopathy	36	9	
Severity of spondyloarthropathy			
Hip disease (yes/no)	9/50	3/16	NS
Erosive arthritis (yes/no)	15/43	0/19	0.036
Extra-articular disease			
Uveitis (yes/no)	13/46	4/15	NS
Psoriasis (yes/no)	20/39	4/15	NS

*A responder was defined as a patient who continued treatment over a six month period, a non-responder as a patient who discontinued treatment because of inefficacy between the fourth and sixth month of treatment.

†Statistical significance was determined by the Wilcoxon test for the continuous variables and the χ^2 test for the dichotomus variables. NS=not significant.

Table 4 Adverse reactions observed in 101 patients with spondyloarthropathy treated with sulphasalazine

Characteristics	No of patients	No of withdrawals*	Time of withdrawal (weeks)
Gastrointestinal disorders	15	8	1,4,4,26,30,30,39,100
Central nervous system disorders			
Insomnia	1	1	1
Dizziness	2	2	4,30
Skin reactions			
Rash	1	1	1
Haematological reactions			
Anaemia	2	2	17,96
Leucopenia	1	0	
Fever	3	2	1,1

*Fourteen patients withdrew from the study because of side effects. Two adverse reactions occurred in the same patient in two instances.

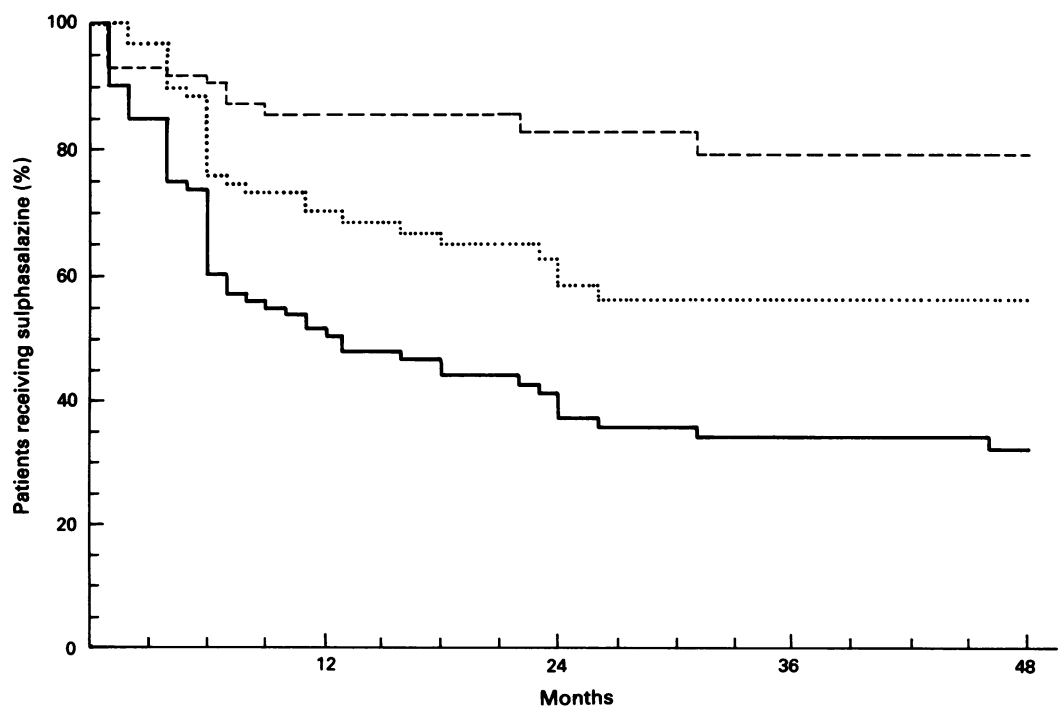
treatment over a six month period (59 patients) and a non-responder was defined as a patient who discontinued treatment because of inefficacy between the fourth and sixth month (19 patients). On the basis of these definitions we could not show a relation between the efficacy of sulphasalazine and either the subgroup of spondyloarthropathy or the clinical presentation of spondyloarthropathy.

Table 4 shows that adverse reactions occurred in 23 patients and resulted in 14 withdrawals. The side effects observed are those usually reported with such treatment. Most of these side effects occurred within the first few weeks (eight patients withdrew from the study because of side effects within the first month of treatment). Such side effects also occurred after a longer period of treatment, however, resulting in eight late withdrawals.

Standard methods of life table analysis were applied to the 101 patients who received sulphasalazine. The end of treatment was taken as the endpoint. Once generated the total termination incidence curve was partitioned according to the main reason for treatment termination: inefficacy or adverse effects. The figure shows the incidence of treatment termination for all reasons, the termination incidence curve for treatment failure, and treatment termination due to adverse effects. By one year 46% of patients receiving sulphasalazine had stopped treatment and by two years 59% of patients had stopped.

Discussion

In this study patients with spondyloarthropathy were treated with sulphasalazine only if their disease was active despite treatment with



Percentage of patients with spondyloarthropathy still receiving treatment with sulphasalazine with respect to inefficacy (.....), side effects (---), and all reasons (—).

optimum doses of NSAIDs. This subgroup of patients represents only 27% of the group of patients with spondyloarthritis treated in this department.

The reasons for treatment with sulphasalazine are based on our experience and knowledge of this drug. We consider sulphasalazine to be a slow acting drug as in a double blind placebo controlled study¹² the group receiving sulphasalazine and the group receiving placebo diverged only after one to three months of treatment. As there are no data suggesting that sulphasalazine is a disease modifying drug in terms of the prevention of spinal ankylosis or the prevention of articular erosions, or both, we do not use this drug in patients who have mild disease or a disease which is well controlled by NSAIDs.

In this retrospective, open, uncontrolled study, we confirmed the favourable effects of sulphasalazine on the activity of the disease. After the first six months of treatment the clinical efficacy of the drug was considered sufficient by the doctor and the patient to be continued in 59 patients. This beneficial effect persisted during a long period of time as suggested by the statistically significant reduction in the efficacy variables between start and end of treatment (see table 2) and as also suggested by the low percentage of patients who had to discontinue the drug after the first six months of treatment (fig).

The side effects observed are those usually reported with sulphasalazine. As previously reported in rheumatoid arthritis,^{23 24} side effects occurred mostly in the first weeks after starting treatment, but some of the severe adverse reactions leading to the discontinuation of the drug occurred some months later (see fig and table 4). These late withdrawals because of toxicity suggest that close monitoring must be carried out as long as treatment is continued.

In this study we could not identify a subgroup of patients who might respond preferentially to treatment with sulphasalazine. These negative results suggest that sulphasalazine might improve the clinical status of patients with active spondyloarthritis whatever the clinical presentation (spinal or peripheral articular disease, or both). The retrospective study design and the possible bias introduced by our definition of responder do not allow any definite conclusion, however, and suggest that further prospective controlled studies of sulphasalazine in the whole group of spondyloarthropathies are necessary to determine the factors predictive of

beneficial treatment with sulphasalazine in patients with spondyloarthritis.

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